REMARKS

Claims 1-8 are pending. Claims 6-8 stand withdrawn by the Examiner. Claims 1 and 4-5 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ratsimamanga et al., U.S. 3,366,669 ['669], and claims 2-3 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ratsimamanga et al. ['669] in view of Mason, Jr. et al., U.S. 4,393,048 ['048]. Applicants respectfully request reconsideration of the above-referenced application in view of the following remarks.

1. Claims 6-8 were withdrawn as directed to an independent invention.

The Examiner asserts that claims 6-8 are directed to an invention that is distinct from the invention as originally claimed. The applicant agrees that the two criteria commonly used to determine if inventions are distinct are that (1) the process for using the product as claimed can be practiced with another materially different product or that (2) the product as claimed can be used in a materially different process. The applicant respectfully asserts that the election/restriction of claims 6-8 was improper because the Examiner did not shown that the inventions are distinct, stating merely that the product as claimed can be used for wound healing.

Such a bare statement does not show that the method claims 6-8 are directed to an invention distinct from the invention claimed in original claims 1-5, so applicants request reconsideration and withdrawal of the restriction requirement.

2. Under 35 U.S.C. 103(a), claims 1 and 4-5 were rejected as being unpatentable over Ratsimamanga et al.['669], and claims 2-3 were rejected as being unpatentable over '669 in view of Mason, Jr. et al., U.S. 4,393,048 ['048].

The Examiner stated that '669 teaches salts of asiatic acid to produce water soluble, wound healing derivatives of asiatic acid. Applicant respectfully disagrees that claims 1

and 4-5 are obvious in light of '669. Ratsimamanga et al. ['669] does not teach the specific salts claimed or their biological or pharmacological properties.

Ratsimamanga et al. ['669] teaches derivatives of asiatic acid including hemisuccinates, hemisuccinate salts with alkali, alkali-earth metal and organic bases, and organic salts of asiatic acid including those of alkylaminoalkanols or dialkylaminoalkanols. '669 recognizes that water insolubility of asiatic acid limits its therapeutic application and teaches away from the use of alkali salts of asiatic acid for local application. See column 1 lines 20-31. '669 does not ascribe any biological or pharmacological relevance to the difference between its various compounds, suggesting that the hemisuccinate salts and organic salts of asiatic acid are pharmacologically equivalent. See column 2 lines 5-15.

Mason Jr. et al ['048] discloses a water-soluble hydrogel formed by an alkali metal alginate and glycerin further comprising biocidal agents such as antibiotics, bactericides, chemotherapeutic agents and drugs. The polysaccharides, and in particular the alginates, are well known gelling agents and widely used for this purpose in compositions of drugs, cosmetics and food.

The present invention of specific asiatic acid species which possess unexpectedly improved pharmacological properties overcomes formulation problems associated with cosmetics or pharmaceuticals. More specifically, the claimed salts are able to form a hydrophylic gel, being sufficient to mix the salts with water (without any excipient or diluent or gelification agent) in a suitable ratio between the salts and the water (see example 7). This property renders the invention useful for the preparation of pharmaceutical or cosmetic topical compositions able to facilitate the hydration of the epidermis. Undoubtedly this result represents an important advantage, being well known that the hydration of the stratum corneum is an

important factor in the topical absorption of an active principle.

Applicant has provided data in the specification observing that the claimed compounds show pharmacological properties over control substances. See page 15. In addition, applicant has caused tests of the claimed compounds to be compared with a compound of the '669 Patent (attached as Exhibit A).

Exhibit A is a study comparing applicants' compounds with compounds of the prior art including the '669 Patent. The study found that applicants' compounds asialene, L-asialene, and madecalene exhibited meaningful anti-inflammatory activity while the activity exhibited by the '669 compound was not meaningful. See Exhibit A Conclusions at pg. 3.

Thus, applicant's compounds have an unexpected property of anti-inflammatory activity not present in the '669 Patent. Given that the claimed salts are not disclosed or obvious, and that they display unexpected efficacy relative to the compounds of '669, applicant respectfully requests reconsideration and withdrawal of the §103 rejections.

CONCLUSION

Based on the foregoing remarks, it is respectfully submitted that the claims as currently pending are patentable and in condition for allowance.

If any issues remain, or if the Examiner has any suggestions for expediting allowance of this application, he is respectfully requested to contact the undersigned at (212) 415-8715.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 0558-4018. **A DUPLICATE OF THIS DOCUMENT IS ATTACHED.**

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: January 14, 2004

By: _____
Katherine S. Brown
Registration No. 54,742

Correspondence Address

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, New York 10154
(212) 758-4800
(212) 751-6849 (facsimile)

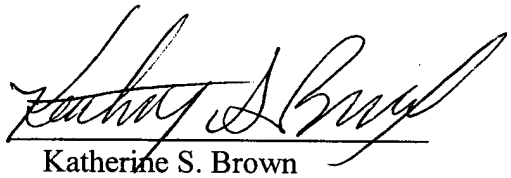
AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 0558-4018. **A DUPLICATE OF THIS DOCUMENT IS ATTACHED.**

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: January 14, 2004

By: 
Katherine S. Brown
Registration No. 54,742

Correspondence Address

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, New York 10154
(212) 758-4800
(212) 751-6849 (facsimile)

UNIVERSITA' DEGLI STUDI DI TRIESTE
Dipartimento di Economia e Merceologia
Delle Risorse Naturali e della Produzione

STUDY OF THE TOPICAL ANTI-INFLAMMATORY ACTIVITY

Introduction

The topical anti-inflammatory activity of the following products at equimolar doses was evaluated at the Department of Economy and Marketing of Natural Resources and Production of the University of Trieste on behalf of Euphar Group srl:

1) Described in the WO 00/63148 Euphar Group srl:
   - Asiatic acid salt with ethylene diamine (example 1 - ASIALENE);
   - Asiatic acid salt with lysine (example 2/5C - L-ASIALENE or LYSALENE);
   - Madecassic acid salt with ethylene diamine (example 4 - MADECALENE).
2) Described in the WO 98/23574 (D2):
   - octyloxymethyl 3,23-O-alkylidene asiatate (example 5, compound 6);
   - ethyloxymethyl 2-deoxy-3,23-O-isopropylidene asiatate (example 12, compound 12);
3) Described in the US PATENT 3.366.669 (D1):
   - 2-2diethylamino-ethyl-hemisuccinate of asiatic acid;

The anti-inflammatory activity of the abovementioned products was compared with the non-steroid, anti-inflammatory drug Indometacin.
The oedema inhibition test caused by the Croton oil in the rat auricle was used as experimental model, whereas the antiedematous effect was evaluated 6 hours after the inflammation induction, that is when the oedema in control animals is maximum (Tubaro et al. – Agents Actions 17: 347-349, 1985).

Materials and Methods

Substances and animals: the abovementioned products were supplied by Euphar Group srl (Piacenza). The Croton oil and Indometacin were purchased at Sigma (Milan), while th ketamine hydrochloride was purchased at Virbac (Milano). The other reagents used are products of analitical grade which were purchased at Carlo Erba (Milano). The animals used are male albinic rats CD-1, whose average weight is 28-32 gramms, purchased at Harlan – Italy (S. Pietro al Natisone, UD).

Inhibition test of the oedema caused by the Croton oil in the rat auricle: the animals were housed in groups of 5 and kept for at least one week in the same environment, where the test was then carried out. The housing environment was kept at constant temperature and relative humidity (23 ± 1°C and 50-60%, respectively), whereas a fixed cycle of artificial lighting was present (6 a.m. – 6 p.m.).
A few minutes before causing the inflammation the animals were anaesthetized with 145 mg/kg ketamine hydrochloride, given through intraperitoneal way. The oedema was induced in the internal surface of the rats right auricle (about 1 cm^2 surface) by applying 80 µg Croton oil and the suitable doses of the substances to be examined dissolved in 15 µl of a ethanol-acetone (3:2) mixture. A solution containing the irritant only was applied to the control animals.

UNIVERSITA' DEGLI STUDI DI TRIESTE
Dipartimento di Economia e Merceologia
Delle Risorse Naturali e della Produzione

6 Hours later the rats were killed and a disk being 6 mm in diameter was punched in both auricles to be weighed. The weight difference between the sample taken from the treated auricle and the one taken from the non-treated auricle gave the extent of the oedematous reaction. The anti-oedematous activity of the examined substance was evaluated on the base of the per cent reduction of the oedema in the treated animals in comparison with the oedema of the control animals.

Statistical analysis: the results were analyzed through the Student's-t test, whereas a $p<0.05$ is considered significant. The dose able to reduce by 50% the oedema (ID_{50}) was calculated through linear interpolation of the oedema inhibition curve.

Results and Discussion

The results relevant to the topical anti-inflammatory activity of the products indicated in the following tables show the inhibition degree of the induced oedema. More in detail, Asialene at the lowest tested dose (30 $\mu g/cm^2$) caused an oedema reduction by 27% while reaching a reduction as high as 94% at 1000 $\mu g/cm^2$ dose. The reference drug Indometacin, applied at 90 $\mu g/cm^2$, reduced the oedema by 49% as it was expected, whereas the Indometacin dose nearest to the one able to reduce the oedema by 50% is equal to ID_{50}=93 $\mu g/cm^2$.

Table 1 : Asialene topical anti-inflammatori activity

SUBSTANCE	DOSE $\mu g/cm^2$	N.an.	OEDEMA (mg) m±es	% RED.
CONTROLS	–	20	6.9±0.2	–
ASIALENE	30	10	5.0±0.4*	27.5
ASIALENE	100	10	2.2±0.5*	68.1
ASIALENE	300	10	0.6±0.1*	91.3
ASIALENE	1000	10	0.4±0.1*	94.2
INDOMETACIN	90	10	3.5±0.4*	49.3

* $p < 0.005$ at the Student's-t test

Table 2 : L-Asialene topical anti-inflammatori activity

SUBSTANCE	DOSE $\mu g/cm^2$	N.an.	OEDEMA (mg) m±es	% RED.
CONTROLS	–	20	7.0±0.4	–
L-ASIALENE	42	10	3.9±0.7*	44.6
L-ASIALENE	141	10	2.6±0.5*	63.5
L-ASIALENE	423	10	0.4±0.2*	94.5
INDOMETACIN	90	10	3.5±0.4*	49.3

* $p < 0.005$ at the Student's-t test

UNIVERSITA' DEGLI STUDI DI TRIESTE
Dipartimento di Economia e Merceologia
Delle Risorse Naturali e della Produzione

Table 3 : Madecalene topical anti-inflammatori activity

SUSTANCE	DOSE µg/cm²	N.an.	OEDEMA (mg) m±es	% RED.
CONTROLS	--	20	6.8±0.3	--
MADECALENE	38	10	4,1±0,6*	39,8
MADECALENE	131	10	2,4±0,3*	64,8
MADECALENE	399	10	0,6±0,6*	91,2
INDOMETACIN	90	10	3.5±0.4*	49.3

* $p < 0.005$ at the Student's-t test

Tabella 4 : Topical anti-inflammatori activity of octyloxymethyl 3,23-O-alkylidene asiatate

SUBSTANCE	DOSE µg/cm²	N.an.	OEDEMA (mg) m±es	% RED.
CONTROLS	--	20	7.1±0.5	--
Octyloxymethyl 3,23-O-alkylidene asiatate	43	10	6,9±0,2*	2,9
Octyloxymethyl 3,23-O-alkylidene asiatate	143	10	6,1±0,3*	14,1
Octyloxymethyl 3,23-O-alkylidene asiatate	426	10	5,7±0,4*	19,8
INDOMETACIN	90	10	3.5±0.4*	49.3

* $p < 0.005$ at the Student's-t test

Table 5 : Topical anti-inflammatori activity of ethyloxymethyl 2-deoxy-3,23-O-isopropylidene asiatate

SUBSTANCE	DOSE µg/cm²	N.an.	OEDEMA (mg) m±es	% RED. %
CONTROLS	--	20	6.8±0.4	--
ethyloxymethyl 2-deoxy-3,23-O-isopropylidene asiatate	39	10	6,4±0,2*	5,9
ethyloxymethyl 2-deoxy-3,23-O-isopropylidene asiatate	129	10	5,7±0,2*	16,2
ethyloxymethyl 2-deoxy-3,23-O-isopropylidene asiatate	389	10	5,3±0,2*	22,1
INDOMETACIN	90	10	3.5±0.4*	49.3

* $p < 0.005$ at the Student's-t test

Tabella 6 : Topical anti-inflammatory activity of 2-2diethylamino-ethyl-hemisuccinate of asiatic acid

SUBSTANCE	DOSE µg/cm²	N.an.	OEDEMA (mg) m±es	% RED.
CONTROLS	--	20	6.9±0.2	--
2-2diethylamino-ethyl-hemisuccinate of the asiatic acid	44	10	6,5±0,3*	5,8
2-2diethylamino-ethyl-hemisuccinate of the asiatic acid	148	10	6,1±0,2*	11,6
2-2diethylamino-ethyl-hemisuccinate of the asiatic acid	445	10	5,6±0,3*	19,8
INDOMETACIN	90	10	3.5±0.4*	49.3

UNIVERSITA' DEGLI STUDI DI TRIESTE
Dipartimento di Economia e Merceologia
Delle Risorse Naturali e della Produzione

* $p < 0.005$ at the Student's-t test

Conclusions

Comparing the topical anti-inflammatory activity carried out by the products described in three different patents gives as a result a remarkable difference as far as the meaningfulness of the evaluated result with reference to the drug Indometacin is concerned and between the aforesaid products themselves.
As a matter of fact as the three products:

- ASIALENE (salt of the asiatic acid with ethylene diamine);
- L-ASIALENE or LYSALENE (salt of the asiatic acid with lysin);
- MADECALENE (salt of the madecassic acid with ethylene diamine);

described on the WO 00/63148 show meaningful results ($p<0,005$), the other tested products, i.e.:

- octyloxymethyl 3,23-O-alkylidene asiatate;
- ethyloxymethyl 2-deoxy-3,23-O-isopropylidene asiatate;

described in the WO 98/23574 and:

- 2-2diethylamino-ethyl-hemisuccinate of the asiatic acid

described in the US PATENT No. 3.366.669 are not meaningful, even if a certain activity has been recorded.
The structure of the three groups of products was examined so as to be able to explain the experiment data. Following on such analysis a main difference came out between the compounds described in the WO 00/63148, which are just salts of the asiatic acid or madecassic acid, in which the carboxylic function is involved in a saline link - that is just a ionic link - in comparison with the compounds described in the WO 98/23574 and USA PATENT No. 3.366.699 describing esters, i.e. derivative esters which means that they change the structure of the asiatic acid involving the hydroxyles present in these natural molecules.
Taking into account the results obtained, it is advisable to keep the original structure of both the asiatic and madecassic acid while improving the solubility with important advantages on the formulation of the products and remarkable anti-inflammatory activity.

Prof. Roberto Della Loggia